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Abstract

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PI Name: YAFFE, MICHAEL B

PI Email: myaffe@mit.edu

Project Title: High Throughput Screening for Inhibitors of the Polo Box Domain of Human Polo-Like kinase 1 (Plk1)

Abstract: *DESCRIPTION (provided by applicant):* The long term goal of this project is to identify lead compounds for anti-cancer drug development that specifically target Polo-like kinase 1 (Plk1). Plk1 is a key regulator of cell division and is highly expressed in many forms of human cancer. We have developed a high throughput fluorescence polarization-based assay to screen for small molecule inhibitors of the Polo box domain (PBD) of Plk1. We previously identified the PBD as a phosphopeptide binding domain and showed that this phosphopeptide binding is essential for Plk1 localization and substrate targeting. The assay utilizes a fluorescently labeled phosphopeptide that exhibits fluorescence polarization (FP) when bound to the PBD. Small molecules that compete with the phosphopeptide for PBD binding will reduce the FP signal. We implemented this assay in a small scale screen of 3,362 compounds. Hit compounds were confirmed using a biochemical assay for inhibition of PBD binding to phospho-protein ligands from cell lysate, and a cell-based assay, which identified one compound that inhibited the proliferation of mammalian cells in culture. However, the chemical properties and aqueous solubility of this compound are not drug-like, and we are therefore proposing to apply our assay to the MLSCN compound collection to identify additional PBD inhibitors with more desirable properties. Hit compounds identified in this primary screen will be confirmed by the secondary assays that we have developed. We will also pursue crystal structures of PBD-inhibitor complexes to facilitate structure-guided optimization of hit compounds. Relevance: Polo-like kinase 1 (Plk1) is an anti-cancer drug target that is essential for the proliferation of tumor cells. Using a rapid high throughput screen of a large collection of small molecule compounds, the proposed study aims to identify specific inhibitors of Plk1, and to conduct follow up studies to help develop these inhibitors into actual anti-cancer drugs.

Thesaurus Terms: anti-cancer, drug development, Polo-like kinase 1, Plk1, fluorescence polarization-based assay, small molecule inhibitors, Polo box domain, PBD, phosphopeptide binding domain, fluorescence polarization, FP, biochemical assay,

inhibition of PBD binding, cell lysate, cell-based assay, Molecular Libraries Screening Centers Network, MLSCN, tumor cells, high-throughput screen, HTS

Institution:	MASSACHUSETTS INSTITUTE OF TECHNOLOGY 40 AMES STREET, BUILDING E18, ROOM 580 CAMBRIDGE, MA 021394307
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